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REMARKS

Claims 1, 4-11, 46, and 47 are pending in this application. Claims 2 and 3 have been cancelled without prejudice. Claims 12-45 have been withdrawn, due to a Restriction Requirement. Claims 7, 8, and 11 have been amended to better define the invention. New Claims 46 and 47 have been added to recite a preferred embodiment of the Applicants' invention. Support for Claims 46 and 47 can be found in the specification, for example, on page 9, lines 12-16. No new matter has been added. Favorable reconsideration and allowance of the subject application are respectfully requested in view of the following comments.

Claim 7 has been rejected under 35 U.S.C. § 112, first and second paragraphs for being indefinite because of the use of the expression "additional medicaments." It is submitted that the expression "additional medicaments" is clear and well known to those of ordinary skill in the art. Solely to expedite prosecution, however, Claim 7 has been amended by replacing the phrase "medicaments" with the term "steroids." Support is found in the specification at, for example, page 7, line 25 through page 8, line 4. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claims 1 and 4-11 have been rejected under 35 U.S.C. § 112, second paragraph for being indefinite for the use of the phrase "17β-estradiol-3-lower alkanoate." Without agreeing with the propriety of the Examiner's rejection, Claims 1 and 5 have been amended to recite 17β-estradiol-3-acetate, a particularly preferred embodiment of the invention. Accordingly, this rejection is rendered moot.

Claims 1-3, 5, 10, and 11 have been rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 3,478,070 (Stein).

Claim 1 recites a pharmaceutical dosage unit for oral administration to a human female. The unit comprises a therapeutically effective amount of 17β-estradiol-3-acetate and a pharmaceutically acceptable carrier.

Stein relates to a process for preparing polyhydroxy 13-alkylgona-(and 8-isogona)-1,3,5(10)-triene 3-ols and Δ^{7}-, $\Delta^{8(9)}$-, $\Delta^{9(11)}$- and $\Delta^{8(9),\,14(15)}$- dehydro analogs thereof by selective acylation in the 3-position. This selective acylation involves reaction with alkali metal lower alkoxide in a lower alkanol, displacement of the lower alkanol with a polar inert solvent and acylation in the solvent. The products of Stein are said to be hormonally active, especially estrogenically and anti-lipemically. The products of Stein are also said to be intermediates in preparing hormonally active steroids, such as 17α-ethinylestradiol (see Col. 1, lines 37-38 and 44-59). Stein teaches (see Col. 1, line 52 and Col. 1, line 70 to Col. 2, line 2) that it is an object of the invention to selectively acylate the 3-position in order to transform other functional groups and to then regenerate the 3-hydroxyl group.

The Office Action suggests Stein for the general teaching of making 3-acylated derivatives of d-estradiol and providing such derivatives in a unit dose form. Example 3 of Stein prepares d-estradiol-3-acetate and Stein mentions its usefulness for the treatment of menopause. (See Col. 6, lines 58-61). The Examiner clearly recognizes that Stein, however, does not disclose a composition comprising a 17β-estradiol-3-acetate. Claim 1 of the present invention is directed to a composition that contains a 17β-estradiol-3-acetate.

Even if Stein can properly be deemed to support a prima facie case of obviousness with respect to a pharmaceutical dosage unit for oral administration containing 17β-estradiol-3-acetate, it is respectfully submitted that any such conclusion is clearly rebutted by the unexpected advantageous properties of the present invention. Most significantly, Applicants have unexpectedly discovered that a 17β-estradiol-3-acetate has an enhanced bioavailability

compared to 17β-estradiol. The Examiner is directed to Example 3 of the present specification, which illustrates the enhanced bioavailability of 17β-estradiol-3-acetate over 17β-estradiol (see Example 3, Table 1). Based on a preliminary evaluation of the data, the inventors reported that the relative bioavailability of estradiol from 17β-estradiol-3-acetate was 15% greater than an equivalent amount of micronized 17β-estradiol, when administered to postmenopausal females. However, upon further evaluation of the data, the relative bioavailability of estradiol in the 17β-estradiol-3-acetate was determined to be higher than originally reported. This is discussed in the accompanying Declaration submitted by Dr. Tina deVries, who is one of the named inventors. In her Declaration, Dr. deVries confirms that the relative bioavailability of estradiol was found to be 19% greater for 17β-estradiol-3-acetate over 17β-estradiol. Thus, the pharmaceutical dosage form of the present invention is clearly and unexpectedly advantageous over the oral administration of a 17β-estradiol containing pharmaceutical composition. Stein clearly does not recognize the unexpectedly higher relative bioavailability of the 17β-estradiol-3-acetate when delivered orally in a pharmaceutical composition. Accordingly, it is respectfully submitted that presently amended Claim 1 is patentable over Stein.

Claims 5, 10, and 11 directly depend from Claim 1. For at least the same reasons discussed above in connection with Claim 1, Claims 5, 10, and 11 are patentable over Stein.

In addition, Claims 4 and 6-9 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 3,478,070 (Stein et al.) in view of an article by Remington, "The Science and Practice of Pharmacy," 19th ed., 1995 (pp. 1413, and 1623-1626) (Remington article) and an article by Wolfe et al., "Effects of Continuous Conjugated Estrogen and Micronized Progesterone Therapy Upon Lipoprotein Metabolism in Postmenopausal Women," Journal of Lipid Research, (2000; 41: 368-375) (Wolfe article). Applicants

respectfully submit that neither Remington nor Wolfe, whether taken alone or together, remedy the deficiencies of Stein.

The Examiner is, with respect, indulging in hindsight analysis by stating that it would be obvious to keep the moisture content below 8% and/or to incorporate an inhibitor of hydrolysis. Stein neither discloses nor suggests that 17β-estradiol-3-acetate is sensitive to hydrolysis. For example, column 6, lines 21-22 teaches that the compounds of Formula I can be formulated in liquid or solid forms – **equal** status is given to these two options. Further on, at column 6, lines 34-45, it is taught that the liquid preparations can be solutions, suspensions or emulsions in a pharmaceutically acceptable carrier such as sterile **water**. An aqueous suspension is specifically taught as being suitable for oral use. Thus, by listing solid and liquid forms as equal alternatives, the problem of achieving a pharmaceutical dosage unit for oral administration comprising a therapeutically effective amount of 17β-estradiol-3-acetate is not even contemplated by Stein.

The Examiner, by rejecting Claims 4 and 6-9 over Stein and further in view of the Remington article and the Wolfe article, suggests that either Stein and Remington or Stein and Wolfe address the same problem. Absent guidance in Stein to consider hydrolysis as an issue, there is nothing to motivate a person skilled in the art to combine the disclosure of Remington or Wolfe with the disclosure of Stein.

The Examiner states that Remington discloses that "silica gel (colloidal silicon dioxide)" is a pharmaceutical ingredient that is used as a tablet moisture adsorber, a glidant and as a suspending and thickening agent. Applicants respectfully submit that this statement is inaccurate. In particular it should be noted that colloidal silicon dioxide is not silica gel – colloidal silicon dioxide is a silica **powder**, a completely different entity which acts as a glidant in promoting flowability of the granulation. On the other hand, silica gels are amorphous forms

of polysilicic acids and are available in various commercials grades of hydration and porosity. Generally, they find use as gas adsorbents, desiccants, thickeners, and gelling agents.

Applicants respectfully submit that there is simply nothing in either Stein or Remington that would have motivated a person skilled in the art to combine the disclosure of Remington with the disclosure of Stein. Moreover, even if combined, there is clearly no suggestion of including an ester hydrolysis inhibitor in the pharmaceutical composition of 17β-estradiol-3-acetate or that the moisture of such a composition be maintained below the recited percent of Claim 4. The Examiner's conclusion that one skilled in the art would use colloidal silicon dioxide to reduce the moisture content of a 17β-estradiol-3-acetate is clearly impermissible hindsight analysis since there is simply no suggestion in Stein to maintain the moisture content of such a pharmaceutical composition below a given level. Accordingly, it is respectfully submitted that Claims 4 and 6 are also clearly patentable.

The Examiner acknowledges that Wolfe is simply cited for the purpose of illustrating that conjugated equine estrogens and micronized progesterone have been previously administered at the same time, whether in the same pharmaceutical dosage unit or in two separate dosage units. Wolfe is entirely silent on the actual pharmaceutical dosage unit(s) being administered. Furthermore, conjugated equine estrogens contain sulfate derivatives, as taught at page 3 of the present description, but do not contain <u>any</u> 17β-estradiol-3-acetate. Applicants respectfully submit an extract from Martindale, the Thirty Second edition, teaching that conjugated estrogens contain 52.5 to 61.5% sodium estrone sulfate and 22.5 to 30.5% sodium equilin sulfate (equilin is 3-hydroxyestra-1,3,5(10),7-tetraen-17-one) and also contains, as sulfate conjugates, 13.5 to 19.5% 17α-dihydroequilin, 2.5 to 9.5% 17α-estradiol and 0.5 to 4.0% 17β-dihydroequilin. Wolfe does not disclose any pharmaceutical dosage unit of 17β-estradiol or any

3-acylated derivative thereof. Furthermore, Wolfe clearly does not disclose any pharmaceutical dosage unit of 17β-estradiol-3-acetate. Thus, Claims 7-9 are clearly patentable.

Wherefore, none of the cited art, whether taken alone or together, discloses or suggests the inclusion of a 17β-estradiol-3-acetate in a pharmaceutical dosage unit, let alone the enhanced bioavailability of a 17β-estradiol-3-acetate. Accordingly, Applicants respectfully requests favorable reconsideration and early passage to issue of the present application.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

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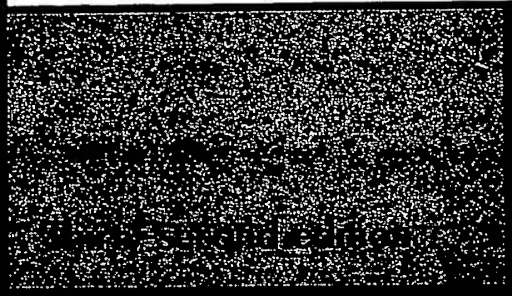
Martindale



Pharmaceutical Press

ponses. Treatment may be aimed at modifying the men-al cycle or treating specific symptoms.[2]

women with predominantly psychological symptoms, in-sing evidence suggests that *selective serotonin reuptake bitors* (SSRIs) may be helpful.[1,3,6-8] Fluoxetine and sertra-e have been shown in controlled trials to alleviate both the chological and somatic symptoms in women with pre-strual syndrome. Buspirone, a serotonin receptor agonist, d clomipramine, a nonselective serotonin reuptake inhibi-have also been tried with some success. The anxiolytic *azolam* has also been used, but use of this and other ben-azepines should be restricted to the luteal phase of the le in selected patients to minimise the risk of dependence d tolerance.[2,6]

dominal bloating and swelling associated with PMS has ditionally been thought to be due to sodium and water re-tion. However, in most women with these symptoms there o evidence of an increase in body-weight or in body sodi-or total water, and use of *diuretics* is therefore not justi-d.[1] Nevertheless, in women with appreciable weight gain in luteal phase diuretics may be useful.[1,6] Another symptom PMS, cyclical mastalgia, is discussed on p.1443.

idoxine has been tried on the basis that it is a cofactor in rotransmitter (specifically serotonin) synthesis, and has n found to relieve depression induced by oral contracep-s in selected patients. However, its efficacy in premen-al syndrome is equivocal, and high daily doses have been ciated with neurotoxicity.[2,6]

atments that modify the menstrual cycle have often been d in women with PMS. In general, drugs with proven effi-y such as danazol, oestrogen implants, and gonadorelin logues are reserved for women with severe PMS unre-nsive to other treatments, because of their adverse effects. *ogestogen* therapy was once popular, but beneficial re-nses have not been universally achieved and the theory t progesterone was necessary to correct a hormone imbal-e is now losing ground. Combined oral contraceptives e met with limited success[1,2,6,8] and in some women, PMS caused or exacerbated by them. Young women with severe ptoms and women approaching the menopause may ben-t from *oestrogen* delivered either as implants or transder-l patches. In women with a uterus, administration with a lical progestogen is required to avoid endometrial hyper-sia which unfortunately, may be associated with the return symptoms, although they may be milder.[1,2] *Danazol* can be eful, but there is concern over its adverse effects on lipids ing long-term use and over the risk of masculinisation of a ale fetus should pregnancy occur. For patients with severe ptoms not amenable to other treatments, gonadorelin an-logues such as *goserelin* can be used to eliminate ovarian ction, 'add-back' treatment with oestrogen plus pro-stogen being given to protect against the side-effects of oes-ogen deficiency including osteoporosis. This treatment is y effective for both physical and psychological symptoms. ort-term use (3 months) of a gonadorelin analogue alone s been used to confirm the diagnosis of PMS, or to predict e response to bilateral oophorectomy.[1,2] Immunological trol using an analogue of *luteinising hormone-releasing rmone* (LHRH) to raise antibodies against natural LHRH d thus suppress ovarian function has also been proposed.

O'Brien PMS. Helping women with premenstrual syndrome. *Br Med J* 1993; 307: 1471–5.
Severino SK, Moline ML. Premenstrual syndrome: identifica-tion and management. *Drugs* 1995; 49: 71–82.
Gold JH. Premenstrual dysphoric disorder. *JAMA* 1997; 278: 1024–5.
Schmidt PJ, *et al.* Differential behavioral effects of gonadal steroids in women with and those without premenstrual syn-drome. *N Engl J Med* 1998; 338: 209–16.
Rapkin AJ, *et al.* Progesterone metabolite allopregnanolone in women with premenstrual syndrome. *Obstet Gynecol* 1997; 90: 709–14.
Mortola JF. A risk-benefit appraisal of drugs used in the man-agement of premenstrual syndrome. *Drug Safety* 1994; 10: 160–9.
Barnhart KT, *et al.* A clinician's guide to the premenstrual syn-drome. *Med Clin North Am* 1995; 79: 1457–72.
Steiner M. Premenstrual syndromes. *Annu Rev Med* 1997; 48: 447–55.

Preparations

P 1998: Estradiol Injection;
SP 23: Estradiol Cypionate Injection; Estradiol Injectable Sus-ension; Estradiol Pellets; Estradiol Tablets; Estradiol Vaginal eam; Estradiol Valerate Injection.

prietary Preparations (details are given in Part 3)
: Climara; Estraderm; Estring; Estrofem; Linoladiol; Progy-; Progynova; Substitol; Systen; Vagifem; Zumenon; *Austral.:* ; Dermestril; Estraderm; Estring; Femtran; Menorest; Pri-gyn Depot; Progynova; Vagifem; *Belg.:* Dermestril; Estra-; Estrofem; Oestrogel; Progynova; Systen; Vagifem; ; *Canad.:* Delestrogen; Estrace; Estraderm; Estring; ; Vivelle; *Fr.:* Benzo-Gynoestryl; Estraderm; Estrofem; ; Oesclim; Oestrodose; Oestrogel; Oromone; Progynova; ; Systen; *Ger.:* Dermestril; Estraderm; Estrifam; Estring; ; Gynokadin; Linoladiol N; Menorest; Progynon Depot 10; Depot 100†; Progynon Depot 40†; Progynova; Tradelia; ; *Irl.:* Climara; Divigel; Estraderm; Estrofem; Evorel; Fe-; Fematrix; Menorest; Oestrogel; Progynova†; Vagifem; : Benztrone; Climara; Dermestril; Epiestrol; Estraderm; Es-trofem; Menorest; Progynon Depot; Progynova; Systen; Vagifem; *Mon.:* Estreva; *Neth.:* Climara; Dermestril; Dimenformon†; Es-traderm; Estring; Estrofem; Meno-implant; Menorest; Progynon Depot 10; Progynon Depot 100†; Progynova; Systen; Vagifem; Zumenon; *Norw.:* Estraderm; Estring; Evorel; Menorest; Progy-nova; *S.Afr.:* Climara; Estraderm; Estring; Estro-Pause; Estrofem; Evorel; Femigel; Menorest; Primogyn Depot; Progynova; Vagifem; *Spain:* Absorlent; Estrotrax; Estraderm; Evopad; Menor-est; Oestraclin; Progynon Depot; Progynova; *Swed.:* Climara; Di-vigel; Estraderm; Evorel; Femanest; FemSeven; Menorest; Oestring; Progynon; Vagifem; *Switz.:* Climara; Estraderm; Es-tring; Estrofem N; Menorest; Oestrogel; Progynon Depot 10; Progynon Depot 100†; Progynova; Systen; Vagifem; *UK:* Cli-maval; Dermestril; Elleste-Solo; Estraderm; Estring; Evorel; Fe-matrix; FemSeven; Menorest; Oestradiol Implants; Oestrogel; Progynova; Sandrena; Vagifem; Zumenon; *USA:* Alora; Climara; Deladiol†; Delestrogen; depGynogen; Depogen; Dioval; Dura-Es-trin†; Duragen†; E-Cypionate†; Esclim; Estra-D†; Estra-L; Es-trace; Estraderm; Estring; Estro-Cyp; Estroject†; FemPatch; Gynogen†; Menaval†; Valergen†; Vivelle.

Multi-ingredient: *Aust.:* Climen; Cyclacur; Dilena†; Estandron; Estracomb; Estragest; Filena; Gravibinon; Gynodian; Ichth-Oestren; Kliogest; Ostrolut; Primodian Depot; Tri-Filena; Triso-quens; *Austral.:* Climen; Divina; Estracombi; Estrapak; Femos-ton; Kliogest; Primodian Depot†; Trisequens; *Belg.:* Climen; Cyclocur; Dimenformon; Diviva; Estracombi; Femoston; Klio-gest; Trisequens; *Canad.:* Climacteron; Estracomb; Neo-Pause†; *Fr.:* Climene; Divina; Fadiamone; Gravibinan†; Kliogest; TOM†; Trisequens; *Ger.:* Acetonal Vaginale†; Alnefug-Emulsion N; Al-picort F; Climen; Crinohermal fem neu; Cyclo-Menorette; Cyclo-Progynova; CycloOstrogynal; Ell-Cranell; Estracomb; Fissan-Brustwarzensalbe†; Gravibinon; Gynodian Depot; Jephagynon; Klimonorm; Kliogest N; Linoladiol-H N; Lynandron†; Mahnt†; NeoOstrogynal; NeyNormin "N" (Revitorgan-Dilutionen "N" Nr. 65); Osmil; Ostronara; Ovaresi†; Primodian Depot†; Primosis-ton†; Procyclo; Sebohermal†; Sisare; Syngynon; Trisequens; *Irl.:* Cyclo-Progynova†; Estracombi; Estrapak; Kliogest; Nuvelle; Tridestra; Trisequens; *Ital.:* Ablacton†; Biormon; Climen; Clym-Depositum†; Cyclacur†; Duo-Ormogyn; Estandron†; Estiamen B†; Estiamen†; Estracomb; Filena; Gravibinan; Gynodian Depot; Kliogest; Menovis; Nuvelle; Primodian Depot†; Trisequens; *Neth.:* Climene; Cyclocur; Divina; Estracomb; Femoston; Klio-gest; Trisequens; Zumeston†; *Norw.:* Cyclabil; Estracomb; Klio-gest; Trisekvens; *S.Afr.:* Climen; Divina; Estracombi; Kliogest; Mixogen; Postoval; Primodian Depot; Trisequens; Trivina; *Spain:* Absorlent Plus; Dinatrofon†; Estandron Prolongado†; Estracomb; Gynodian Depot; Progyluton; Topasel; *Swed.:* Cyclabil; Divina; Estracomb; Femanor; Femasekvens; Kliogest; Trisekvens; Trivi-na; *Switz.:* Alpicort F; Climen†; Cyclacur; Estandron Prolonga-tum†; Estracomb; Gravibinon†; Gynodian Depot; Kliogest; Linoladiol; Primodian Depot†; Primosiston; Triaval; Trisequens; Tyficuline†; *UK:* Climagest; Climesse; Cyclo-Progynova 1 mg; Cyclo-Progynova 2 mg; Elleste Duet Conti; Elleste-Duet; Estra-combi; Estrapak; Evorel Conti; Evorel Sequi; Evorel Pak; Fema-pak; Femoston; Hormonin; Kliofem; Kliovance; Nuvelle; Nuvelle TS; Tridestra; Trisequens; *USA:* Andro/Fem†; Deladumone†; de-pAndrogyn; Depo-Testadiol; Depotestogen; Duo-Cyp; Durat-estrin; Estra-Testrin†; T-E Cypionate†; Test-Estro; Testaval 90/4†; Valertest.

The symbol † denotes a preparation no longer actively marketed

Oestriol (9090-f)

Oestriol *(BAN)*.

Estriol; Follicular Hormone Hydrate; Theelol. Estra-1,3,5(10)-triene-3,16α,17β-triol.

$C_{18}H_{24}O_3$ = 288.4.

CAS — 50-27-1.

Pharmacopoeias. In *Eur.* (see p.viii), *Jpn*, and *US*.

A white or practically white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, in dioxan, in ether, and in vegetable oils. Store in airtight containers.

Oestriol Sodium Succinate (10345-s)

Oestriol Sodium Succinate *(BAN)*.

Disodium 3-hydroxyestra-1,3,5(10)-triene-16α,17β-diyl disuccinate.

$C_{26}H_{30}Na_2O_9$ = 532.5.

CAS — 113-22-4.

Oestriol Succinate (10068-b)

Oestriol Succinate *(BAN)*.

Estriol Succinate *(rINN)*. 3-Hydroxyestra-1,3,5(10)-triene-16α,17β-diyl di(hydrogen succinate).

$C_{26}H_{32}O_9$ = 488.5.

CAS — 514-68-1.

Oestriol is a naturally occurring oestrogen with actions and uses similar to those described for oestradiol (p.1455). It is claimed to have only a mild proliferative effect on the endometrium.

It is used for menopausal hormone replacement therapy (HRT) (see p.1434). When oestrogens are administered to women with a uterus, a progestogen is required, particularly if used long-term. For short-term treatment, doses by mouth have been 500 μg to 3 mg daily given for one month followed by 500 μg to 1 mg daily. Oestriol has also been given in combination with other natural oestrogens such as oestradiol and oestrone (p.1458); usual doses of oestriol have ranged from about 250 μg to 2 mg daily. It has also been administered intravaginally for the short-term treatment of menopausal atrophic vaginitis as a 0.01% or 0.1% cream or as pessaries containing 500 μg.

Oestriol succinate has also been given by mouth in the treatment of menopausal disorders. The sodium succinate salt has been administered parenterally in the treatment of haemorrhage and thrombocytopenia.

Preparations

Proprietary Preparations (details are given in Part 3)
Aust.: Ortho-Gynest; Ovestin; Styptanon; *Austral.:* Ovestin; *Belg.:* Aacifemine; Ortho-Gynest; *Fr.:* Ovestin†; Physiogine; Synapause†; Trophicreme; *Ger.:* Cordes Estriol; Gynasan; Hormomed†; Klimax-E†; OeKolp; Oestrilin N†; Oestro-Gynaedron M; Orgastyptin†; Ortho-Gynest; Ovestin; Ovo-Vinces; Synapause E; Synapause†; Vago-med†; Xapro; *Irl.:* Ortho-Gynest; Ovestin; *Ital.:* Colpogyn; Ortho Gynest Depot; Ovestin; *Jpn:* Estriel†; *Neth.:* Ortho-Gynest†; Ovestin†; Synapause-E₃; *Norw.:* Ovesterin; *S.Afr.:* Synapause; *Spain:* Ovestinon; Synapause; *Swed.:* Ovesterin; Triovex†; *Switz.:* Klimadoral†; Oestro-Gynaedron Nouveau; Ortho-Gynest; Ovestin; Styptanon†; *UK:* Ortho-Gynest; Ovestin.

Multi-ingredient: *Aust.:* Gynoflor; *Belg.:* Gynoflor; *Fr.:* Trophigil; *Ger.:* Cyclo-Menorette; CycloOstrogynal; Gynoflor; NeoOstrogynal; OestroTricho N†; Oestrugol N; *Ital.:* Estiamen B†; Estiamen†; *Switz.:* Gynoflor E; Trisequens; *UK:* Hormonin.

Conjugated Oestrogens (9091-y)

Conjugated Estrogens.

Pharmacopoeias. In *US*.

A mixture of sodium oestrone sulphate and sodium equilin sulphate, derived wholly or in part from equine urine or synthetically from oestrone and equilin. It contains other oestrogenic substances of the type excreted by pregnant mares. The USP substance contains 52.5 to 61.5% of sodium oestrone sulphate and 22.5 to 30.5% of sodium equilin sulphate; the total of the two combined should comprise not less than 79.5% of the labelled content of conjugated oestrogens. The USP also states that it should contain, as sulphate conjugates, 13.5 to 19.5% of 17α-dihydroequilin, 2.5 to 9.5% of 17α-oestradiol, and 0.5 to 4.0% of 17β-dihydroequilin, relative to the labelled content of conjugated oestrogens.

If it is obtained from natural sources it is a buff-coloured amorphous powder which is odourless or has a slight characteristic odour; the synthetic form is a white to light buff-coloured crystalline or amorphous powder, odourless or with a slight odour. Store in airtight containers.

Adverse Effects and Precautions

As for oestrogens in general (see Oestradiol, p.1455). See also under Hormone Replacement Therapy, p.1435.

Effects on the cardiovascular system. Treatment of men with a previous myocardial infarction with conjugated oestrogens 5 mg daily in the USA Coronary Drug Project was discontinued because of a higher incidence of subsequent coronary events.[1] Moreover, treatment with the lower 2.5 mg dose was later also discontinued because of suggestions of adverse trends including a greater incidence of venous thrombo-embolism.[2] However, observational studies of menopausal hormone replacement therapy indicate that in postmenopausal women there is a reduction in risk of coronary heart disease (see p.1436).

1. Coronary Drug Project Research Group. The Coronary Drug Project: initial findings leading to modifications of its research protocol. *JAMA* 1970; 214: 1303–13.
2. Coronary Drug Project Research Group. The Coronary Drug Project: findings leading to discontinuation of the 2.5-mg/day estrogen group. *JAMA* 1973; 226: 652–7.

Effects on the gallbladder. Analysis of data obtained during the Coronary Drug Project indicated a significant increase in the development of gallbladder disease among men treated with conjugated oestrogens 2.5 and 5 mg daily, compared with those treated with placebo.[1]

1. The Coronary Drug Project Research Group. Gallbladder disease as a side effect of drugs influencing lipid metabolism: experience in the Coronary Drug Project. *N Engl J Med* 1977; 296: 1185–90.

Effects on the nervous system. Reversible chorea developed in a 57-year-old woman receiving conjugated oestrogens and norgestrel;[1] the woman had a history of migraine and Sydenham's chorea.

1. Steiger MJ, Quinn NP. Hormone replacement therapy induced chorea. *Br Med J* 1991; 302: 762.

Hypersensitivity. A report of an anaphylactic reaction following the intravenous administration of conjugated oestrogens.[1]

1. Searcy CJ, *et al.* Anaphylactic reaction to intravenous conjugated estrogens. *Clin Pharm* 1987; 6: 74–6.

Interactions

See under Hormone Replacement Therapy, p.1437.